PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4 -32590A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 03/03257	International filing date *(day/month/year)* 17.07.2003	Priority date *(day/month/year)* 19.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/506		
Applicant LUDWIG INSTITUTE FOR CANCER RESEARCH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.02.2004	17.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Paul Soto, R Telephone No. +49 89 2399-7346

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/03257

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-15 as originally filed

Claims, Numbers

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 3-11 (industrial applicability)

   because:

   ☒ the said international application, or the said claims Nos. 3-11 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-12
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-12
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-2,12; for 3-11 see separate sheet
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 3-11 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. The documents referred to in this report as **D1-D5** are those cited in the Search Report, namely:

D1: SOROKIN PATRICIA: "New agents and future directions in biotherapy." CLINICAL JOURNAL OF ONCOLOGY NURSING. UNITED STATES 2002 JAN-FEB, vol. 6, no. 1, January 2002 (2002-01), pages 19-24, XP009020972 ISSN: 1092-1095

D2: PEDLEY R BARBARA ET AL: "Eradication of colorectal xenografts by combined radioimmunotherapy and combretastatin A-4 3-O-phosphate" CANCER RESEARCH, vol. 61, no. 12, 15 June 2001 (2001-06-15), pages 4716-4722, XP002261294 ISSN: 0008-5472

D3: KINUYA SEIGO ET AL: "Efficacy, toxicity and mode of interaction of combination radioimmunotherapy with 5-fluorouracil in colon cancer xenografts" JOURNAL OF CANCER RESEARCH AND CLINICAL ONCOLOGY, vol. 125, no. 11, November 1999 (1999-11), pages 630-636, XP002261295 ISSN: 0171-5216

D4: WANG D-S ET AL: "ENHANCEMENT OF THE ANTITUMOR EFFECT OF GAMMA-RAY IRRADIATION IN COMBINATION WITH CAMPTOTHECIN AGAINST HUMAN COLORECTAL ADENOCARCINOMA" BIOLOGICAL & PHARMACEUTICAL BULLETIN (OF JAPAN), PHARMACEUTICAL SOCIETY OF JAPAN, JP, vol. 19, no. 3, 1996, pages 354-359, XP001094169 ISSN: 0918-6158

D5: LE COUTRE PHILIPP ET AL: "Effects of the tyrosine kinase inhibitor STI571 and ionizing radiation on a human glioblastoma cell line: Potential use as a

radiosensitizer." BLOOD, vol. 98, no. 11 Part 2, 16 November 2001 (2001-11-16), page 179b, XP009021006 43rd Annual Meeting of the American Society of Hematology, Part 2;Orlando, Florida, USA; December 07-11, 2001 ISSN: 0006-4971

If not indicated otherwise, the relevant passages are those mentioned in the International Search Report.

3. The present application relates to:

(I) the use of the benzamide compound I of the given structure for the manufacture of pharmaceutical compositions for enhancing the effect of radioimmunotherapy of tumours (**claim 1**);

(ii) a combination which comprises (a) N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine and (b) a radioimmunoconjugate agent (**claim 2**);

(iii) a method of treating a human suffering from tumours and who is subjected to radioimmunotherapy, which comprises administering a dose of compound I for enhancing the effect of radioimmunotherapy (**claim 3**);

(iv) a method of treating a warm-blooded animal, especially a human having a tumour comprising administering the combination referred to in claim 2 (**claim 10**);

(v) a kit for radioimmunotherapy comprising (a) a radioimmunoconjugate agent which specifically binds to a tumour-associated antigen, and (b) compound I (**claim 12**).

4. The present application meets the requirements of the PCT with respect to novelty (Art. 33(2)), because none of the documents of the prior art discloses a therapy combining a radioimmunoconjugate and Compound I (Imatinib) for the treatment of solid tumours.

5. The present application does also meet the requirements of the PCT with respect to inventive step (Art. 33(3)) for the following reasons. Therapies for the treatment of solid tumours, and more in particular colorectal cancers, combining a radioimmunoconjugate and another agent are known from the prior art. **D2** discloses a combination of radioimmunotherapy with Combretastatine A-4 3-0-Phosphate, an antivascular agent (DMXAA is also discussed); **D3** discloses radioimmunotherapy of colon cancer combined with 5-fluorouracil. **D4** discloses the enhancement of the antitumor effect of radioimmunotherapy with camptothecin in the treatment of colorectal adenocarcinoma. The present application differs from these therapies in that radioimmunotherapy is combined with a different agent, namely with Imatinib.

Thus, the **problem** to be solved by the present application is the provision of an alternative agent enhancing the antitumor effect of radioimmunotherapy in the treatment of colorectal cancer. The **solution** provided by the present application involves an inventive step because no indication has been found in the prior art which would prompt the skilled person to select Imatinib in order to solve the problem posed. In particular **D5** discloses that STI571 (Imatinib) potentiated the effects of ionizing radiation on a human glioblastoma cell line but not on mamma or colorectal carcinoma cell lines. Thus, this document rather leads the skilled person away from the solution provided by the present application.

6.1. Present claims 2 and 12 meet the criterion set forth in Article 33(4) PCT because their subject-matter is susceptible of industrial application.

6.2. For the assessment of the present claims 1 and 3-11 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

7. For the sake of completeness the following observations are made:

(I) It is clear from the application as a whole, and more in particular from the description (see in particular from page 1-paragraph 2 to page 2-paragraph 4, paragraph 4 in page 3, paragraph linking pages 6-7) that the feature for the tumours being "solid" tumours is essential to the definition of the invention. Since independent claims 1, 2, 3, 10 and 12 do not contain this feature they do not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

(ii) Present claims 2 and 12 are directed to a combination and a kit, respectively, which comprise the two specified agents for simultaneous, separate or sequential use. However, said claims do not include in their formulation the indication of purpose for the combined therapy. In that case, said claims are regarded as a mere association of known components without a functional unity because there is not necessarily a direct interaction between the physically separated components. Said claims would

therefore lack novelty over the individual components. In order to re-establish novelty, said claims should be redrafted by explicitly stating their therapeutical indication, for example the treatment of a colorectal or a solid tumour. The present opinion relating to novelty of the claims applies only if this prerequisite is fulfilled.